IN THE UNITED STATES PATENT & TRADEMARK OFFICE

In re Application of
Berndl et al.
Serial No. 09/937,313
Filed: September 24, 2001
For: Solubilizing excipients in powder form for solid pharmaceutical presentations

D E C L A R A T I O N

I, Karl Kolter, Dr. rer. Nat., a citizen of Germany and a resident of Sudetenstrasse 1, 67117 Limburgerhof, Germany, hereby declare and say as follows:

I am a fully trained pharmacist, having studied pharmacy at Mainz University in the period of from 1976 to 1981.

I was awarded my PhD in Mainz, where in the period of from 1981 to 1985 I worked as an assistant at Mainz University.

I joined Knoll AG, a former subsidiary of BASF Aktiengesellschaft, located in 67061 Ludwigshafen, in 1986 , where I have been engaged in research and development in the field of pharmaceutical formulations.

In 1993 I joined BASF Aktiengesellschaft, now named BASF SE, and I have since been engaged in the field of development of pharmaceutical excipients and formulations of active ingredients.

I have carefully studied the final Office Action of May 28, 2008 and the rejection of the claims under 35 U.S.C. § 103(a).

Now, hereby, I want to state the following:

First of all I want to explain about the specific features of the invention and the problems associated therewith.

The claimed invention is concerned with providing for an enhanced method for handling liquid or semi-solid surface-active substances in connection with the manufacture of solid pharmaceutical dosage forms. The claimed method aims at producing an excipient rich in liquid and semi-solid surface-active substances.

Liquid and semi-solid surface-active substances and pharmaceutical formulations comprising such substances are often difficult to handle because of the wax-like and sticky consistency of the masses. These surface-active substances also have a plastifying effect. Especially in case of formulation mixtures for direct compression to tablets such surface-active substances have hitherto caused problems.
It is also noteworthy that the excipient according to the claimed invention which consists essentially of two components, i.e. the liquid or semi-solid surface-active agent and a polymer, forms a coherent water-soluble polymer-surfactant phase.

It was unexpected that the excipients obtained either by spray-drying or by melt extrusion turned out to be free-flowing powders that can easily be processed without restriction to give solid dosage forms. Furthermore it was unexpected that the excipients could be processed by spray-drying. An ordinarily skilled expert would certainly have expected that especially spray-drying of a solution of the two specific components in the claimed amounts would not work at all because of the plastifying properties of the surface-active substances.

The excipient obtained by the claimed process is specifically suitable for use as a solubilizer in pharmaceutical formulations of in water insoluble or sparsely soluble active ingredients.

As regards the claim rejections of cClaims 10-12, 14-18, 20 and 22-24 over Guzi et al. in view of Staniforth et al. or Zeligs et al. I want to state as follows:

According to the position expressed in the Office Action of May 24, 200, page 2, last ^{t} paragraph) the Guzi et al. reference (US 4,127,422) teaches a method of making an excipient comprising spray-drying a solution comprising 15-40 % b.w. of a nonionic dispersing agent and a N-Vinylpyrrolidone polymer and the excipient is said to comprise (according to the examples) a pigment.

However, the pigment composition disclosed in this document contains 55 -80 % b.w. of a pigment as an obligatory component , i.e. of an ingredient insoluble under aqueous conditions. The amount of 15-40 % b.w. of surfactant cited in the reference is based on the pigment and not on the overall composition (Claim 1 and col. 3, line 44-51).

The water-insoluble pigment is dispersed in an aqueous medium together with a surface-active substance and a polymer. This dispersion is dried by a spray-drying process. The resulting pigment preparation is a non-water soluble system consisting of pigment particles coated with surface-active substance and polymer. Since the spray-dispersion contains such a high amount of solid pigment particles spray-drying is not considered as a problem by a skilled expert.

Apart from that Guzi et al. relates to pigment compositions for use in textile products or paper paints. A skilled expert in the art of making pharmaceutical formulations considers this as a different technical field and would not look for guidance in such a document.

Thus, the method according to Guzi et al. differs not only in the technical field but also in the overall composition, in the morphology of the resulting product (non-water-soluble two phase system according to Guzi et al.versus water-soluble polymer-surfactant phase according to the claimed method) and in the fact that Guzi et al. does not disclose the spray-drying of a solution but the spray-drying of a dispersion with a high content of solids.

Staniforth et al. (US 5,858 ,412) wants to solve a problem in connection with the use of high amounts of microcrystalline cellulose in a formulation, because the loss of compressability of microcrystalline cellulose when used in wet granulation has long been considered as a problem (see col.3, l. 53-56, and col.4, l.38-47). In order to overcome this problem Staniforth combines the microcrystalline cellulose with a compressibility augmenting agent such as preferably silicon dioxide or a surfactant with a HLB > 10, preferably SDS.

The Examiner argues that it would be obvious to include the surfactants disclosed by Zeligs et al. (US 6,086,915) into the process taught by Staniforth in order to improve the compressibility of the resulting microparticles.

However, the presently claimed process is not directed at improving the compressability of the particles, but at finding an improved method for handling larger amounts of liquid or semisolid surfactants.

Secondly, the problem underlying Staniforth's process is caused by the specific surface properties of microcrystalline cellulose. In other words the technical effects and results described Staniforth are invariably linked to the specific properties of microcrystalline cellulose. Therefore a skilled person trying to find an improved method for combining higher amounts of certain surfactants with the water-soluble N-Vinylpyrrolidone polymer will not consider the process taught by Staniforth as relevant, because Staniforth's process completely depends on the properties of the water-insoluble microcrystalline cellulose and its surface properties.

Insofar it was unexpected that the claimed method could be successfully used for making the claimed excipients rich in liquid or semi-solid surface-active substances and in form of a free-flowing powder that can be easily processed in a direct-compression tabletting process

As regards the rejection of Claims 10, 15, 16, 18, 20 and 21 over Kolter et al. (US 6,066,334) in view of Staniforth et al. and Zeligs et al., the It was argued in the Office Action that it was obvious to combine the surfactants of Staniforth et al. and Zeligs et al. in order to provide an improved method of making carrier composition with improved stability.

However, the Kolter et al reference relates to compositions having important different features. The redispersible polymer powders according to Kolter et al. comprise a binder consisting essentially of polyvinyl acetate and an N-vinyl pyrrolidone-containing polymer. Preferably the binder consists of 80 %b.w. of polyvinyl acetate and 20 % b.w. of polyvinyl pyrrolidone as exemplified by Ex. 1, 2 or as claimed in claim 4. It is an essential feature of that teaching that a major component of the redispersible polymer powder is formed by the non-water-soluble polyvinyl acetate. These binder compositions are two-phase systems because polyvinyl acetate and the N-vinylpyrrolidone polymers are not miscible.

By consequence, a mere inclusion of surfactants known from Staniforth et al. and/or Zeligs et al. and optimization of the amount of dispersant would not lead to the claimed invention. There is no motivation for the skilled artisan to adapt the amount of dispersant and at the same time to delete the most important polymer component from the composition. In addition, the teaching of Kolter et al. is directed at providing improved binders for instant release. Also, the polymer composition according to Kolter et al. is a two-phase system which can be used as a binder and which does not have a solubilizing effect. Improving the processability of the excipient with regard to stickiness is of no concern to Kolter et al., since this problem does not occur due to the essentially different composition and morphology of the binder.

Insofar a skilled person would neither have the motivation to combine the cited references in such a way nor would such a combination lead to the claimed invention. I want to state again that it was quite unexpected for the skilled expert that the claimed method could be successfully applied to give free-flowing powders.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so are made punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed at 67056 Ludwigshafen, Germany, this 16th day of October 2008.

Signature of Declarant